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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,922	04/05/2001	David E. Comings	1954-332	3812

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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/22/2002 11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,922	COMINGS, DAVID E.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *16-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, Claims 1-15 in Paper No. 11 is acknowledged. Applicant's do not traverse the restriction between the various groups. However, Applicant's traverse the restriction to a single gene. The response asserts that Claims 2 and 3 are directed to combinations which require all or more than one of the genes which indicates greater risk for ADHD. These arguments have been thoroughly reviewed. While the examiner maintains that each of the genes are distinct from each other and each of the combinations of genes are distinct from one another, solely to advance prosecution, the examiner has searched each of the recited genes and the combinations. However, this withdrawal of restriction for Group I, does not preclude the examiner from maintaining and deeming the restriction to a single gene or single combination of genes in other groups a burden.

Therefore, the restriction is made FINAL.

Priority

2. This application claims priority to provisional application 60/195,312, filed April 10, 2000.

Drawings

3. The drawings are approved by the examiner.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method of determining a risk of an individual for attention deficit hyperactivity disorder (ADHD) by determining whether a subject has a non-wild-type allele from at least one gene selected from TPH, PNMT, ADOA2A, NOS3 and NAT1.

The specification teaches analyzing numerous genes for their association with ADHD. Figure 1 illustrates the ANOVA of ADHD scores for 40 genes. Figure 1A-2 teaches TPH SNP A779C has a p values of 0.495. Figure 1A-3 teaches PNMT GNP G-148A has a p value of 0.129. Figure 1B-2 teaches ADORA2A C108T (Rsal) has a p-value of 0.229. Figure 1B-2 teaches NOS3 has a p value of 0.830. Finally, Figure 1B-3 teaches NAT1 T1088 have a p value of 0.329. It is noted that none of these p-values are significant at alpha= 0.05. Figure 2 appears to illustrate 22 genes when combined are associated with ADHD, however, it is unclear which 22 genes are involved in the analysis. Figure 3 appears to illustrate that each of TPH, PNMT, ADOA2A, NOS3 and NAT1 have a p values <= 0.05 for ADHD. Thus, there is apparent confusion between Figure 3 and Figure 1. The specification teaches there were 326 unrelated, non-Hispanic Caucasians. 271 of the subjects have Tourette syndrome and 55 were controls (page 9, lines 20-25). The text of the specification teaches ADOA2A was significant at $p < 0.05$ (page 12, lines 15-18). Moreover, the specification teaches that "the only other new gene that produced a significant individual result was the NAT1

gene" (page 13, lines 10-11). With respect to NOS3, the specification teaches that NOS3 was significantly involved with all three traits" (page 15, lines 54-28).

The art teaches analysis of numerous genes in ADHD including ADOA2A, NAT1 and NOS3. Comings (Clin. Genet. Vol. 58, pages 31-40, July 2000) teaches each of these genes are not significantly associated with ADHD (Table 1). With respect to TPH, the art teaches there is a lack of association between the A218C polymorphism and ADHD in Chinese Han population. Tang (Am. J. of Med. Genetics, Vol. 105, pages 485-488, August 2001) teaches that the negative results of the study may be limited to the Chinese Han population or that the A218C polymorphism is not functionally significant and that some other variants are associated with ADHD (page 487, col 1-2).

The art also teaches that ADRA2A and ADRA2C genotypes are individually associated with ADHD (Comings et al. Clin. Genet. Vol. 55, pages 160-172, 1999, Table 2, page 165).

Moreover, Blum (US Pat. 6,132,724, October 2000) teaches association of CHRNA4 gene with ADHD (Example 28, col. 306). Similarly, Blum teaches the additive effect of three adrenergic genes (ADRA2A, ADRA2C, DBH) on ADHD subjects (Example 27, col. 294).

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. Based upon the teachings in the specification, it is unclear how to interpret the data. For example, the figures appear to illustrate that the genes are both significant and not significant. Therefore, it is unclear what is being shown in the figures and whether the genes are significant alone, i.e. not in combination

with other genes. Moreover, it is unclear whether each of the combinations of gene are significantly associated with ADHD, or whether only the combination of 22 genes is significantly associated with ADHD.

Additionally, the claims are drawn to detecting a non-wild-type allele in the recited genes. The specification and the art have taught either a single SNP per gene or a couple of SNPs. The specification has not described which non-wild-type alleles are associated with ADHD and which alleles are neutral polymorphism. Numerous SNPs in the genome are known to be unassociated with diseases, especially with ADHD in particular. Therefore, the mere detection of a non-wild-type allele within TPH, PNMT, ADOA2A, NOS3 or NAT1 does provide indication that the subject is at an increased risk for ADHD. The specification has examined SNP A779C within TPH gene; SNP G-148A within PNMT; SNP C108T (RsaI) within ADOA2A; and T1088A within NAT1. These specific mutations are not representative of all non-wild-type alleles within the genes. In order to practice the invention as broadly as claimed the skilled artisan would be required, unduly, to analyze the recited genes for alleles, determine whether they are wild-type or non-wild-type alleles and analyze the alleles for an association with ADHD. This trial and error experimentation is unpredictable. It is unpredictable whether the gene has alleles aside from the alleles studied in the instant application, whether these alleles are associated with ADHD, and whether the alleles confer an increased risk for ADHD or whether the alleles are protective and in fact are indicative of a decreased risk for ADHD. Moreover, the skilled artisan would be required to analyze numerous populations which are representative to determine

whether the allele is associated with an increased risk over populations in general or whether the allele is associated within only certain populations. For example, in the instant case, in the event that the TPH gene A218C polymorphism is associated with non-Hispanic Caucasians, as asserted in the specification, the art teaches that there is no association in Chinese Han populations. Moreover, the specification teaches that there are differences in associations between various ethnic or racial backgrounds (page 7). The specification has only sampled unrelated non-Hispanic Caucasians. The specification has not provided a broad based population study which would be representative of numerous populations.

With respect to Claim 9, the claimed method appears to be solely directed to a research project to determine which alleles or polymorphisms are associated with a trait and in the event that there is a positive association, the polymorphisms will be added to the array of polymorphisms to be studied. This method directed to trial and error experimentation would require the skilled artisan to perform all of the necessary work to carry out a useful method. The specification nor the art provides guidance to selecting and identifying unknown polymorphisms within a gene which are positively correlated with a trait. Therefore, the entire method would be a research project where the results of the method are unknown at the time the invention was made. There is not predictable results which would allow the skilled artisan to practice the claimed invention.

With respect to Claims 10-15, the claims are drawn to methods of determining a treatment modality by detecting non-wild-type alleles wherein said treatment is based

upon which of said genes are non-wild-type. Neither the specification nor the art provide guidance to determining treatment based upon the detection of non-wild-type alleles. It is unclear whether the claim is intended to be directed to administering treatment when there is an increased risk for the disease or whether the claim is directed to administering specific treatments based upon the alleles present. In the latter case, it is unclear which treatments would be suitable for which non-wild-type alleles and which of these treatments would be unsuitable for which alleles. If differential treatment is required by the claims depending on the alleles present, the specification nor the art provides any guidance to generating differential treatment regimes for the different alleles. The skilled artisan would be required to perform undue experimentation to research which alleles were positively treated with certain treatments and which alleles were non-responsive to certain treatments.

Therefore, based upon the analysis above, neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1-8 are indefinite over the recitation "said gene" because the claim is drawn to "at least one gene". Therefore, in the event that the embodiment directed to three genes is examined, it is unclear what "said gene" is referring to. The claim may be amended to clarify that the detection of one or more non-wild-type alleles is indicative of an increased risk.

B) Claim 9 is indefinite because the claim is unclear. The claim is for developing an assay that is diagnostic for attention deficit hyperactivity disorder, but the first step requires identifying a trait to be studied. It is unclear if the method is for developing an assay for ADHD, what trait is to be studied aside from ADHD.

C) Claims 10-15 are indefinite over the recitation "wherein said treatment modality is based upon which of said genes are non-wild-type" because it is unclear how to practice the method one the genetic profile of the subject is obtained. Once the genetic profile of the subject is determined to be non-wild-type, it is unclear what treatment modality is claimed. It is unclear whether any treatment is acceptable or whether specific treatments are acceptable only to certain non-wild-type alleles or certain combinations of non-wild-type alleles.

Conclusion

6. No claims allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of formal matters can be directed to the patent analyst, Pauline Farrier, whose telephone number is (703) 305-3550.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
July 17, 2002

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600